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RESEARCH ARTICLE

EFFECT OF NEOADJUVANT THERAPY ON TUMOR SIZE REDUCTION IN BREAST CANCER

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ABSTRACT

The study is carried out as retrospective and prospective observational studies to analyze the cancer characteristics, therapeutic approaches and the state of depression in Breast cancer patients. Breast cancer is one of the highly prevalent female specific carcinomas, however, the rarity of male breast cancers is observed. Neoadjuvant chemotherapy (NAC) has been shown to be a useful strategy in the treatment of Locally advanced breast cancer (LABC) because it results in tumor downstaging benefits. This study agrees with what Chintamani *et al*. found in India in a study population with similar characteristics and the same chemotherapy regimen. Neoadjuvant chemotherapy has proved appealing potential benefits over the classic adjuvant therapy. Apart from cancer characteristics and therapeutic statistics, the effects of Doxorubicin neoadjuvant therapy were analyzed with respect to tumor size after each cycle of NAC. The significant change in the tumor size (measured in cm) of 39 patients undergoing NAC. The use of Doxorubicin for neoadjuvant therapy was found to be significantly beneficial in the reduction of tumor size of locally advanced breast cancers (LABC). This reduction in tumor size prior surgery helps in the choice of type of surgery being performed. It can result in avoiding the use of mastectomy and more preference for breast-conserving surgeries can be given.

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INTRODUCTION

The Number of cases reported from developed regions (794000) is notably less significant than the cases reported from the less developed regions (883000 cases) (Malvia, 2017). Treating Locally Advanced Breast Cancer (LABC) to improve the mortality rate remains a challenging task. Implementing neoadjuvant therapeutic regimens have shown remarkable results in reducing the tumor size and minimizing further complications (Rastogi, 2008; Maráz, 2005 and Beriwal, 2006). There is no defined neoadjuvant therapeutic regimen, but the usual typical implementation consists of a minimum of 4 to a maximum of 6 cycles of anthracycline-based therapy (Powles, 1995 and Lee, 2007). Chintamani et.al studied for the characteristics and outcomes of chemotherapy in Indian populace to find a variation of 30% tumor reduction to 70% desired clinical outcome achievements (Chintamani, 2004).

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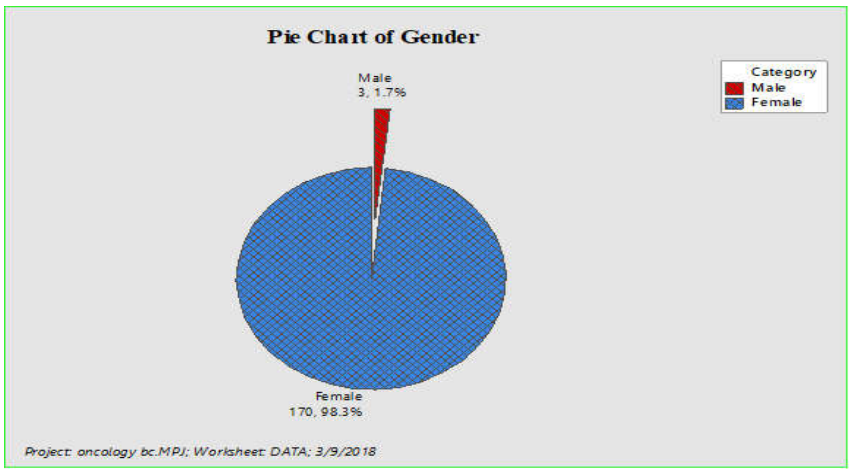
In another study by Moon et.al from Korea, reported an outcome rate of 84.4% for breast carcinomas having a pCR rate of 25.6% (Moon, 2006). The Clinical responses of other studies done by Rastogi et.al (Rastogi, 2008), and Fisher et.al [9] showed clinical responses of approximately 85% and 79% respectively, having pCR rates of 40% and 36% by the end of initial 4 cycles of neoadjuvant therapy based on anthracyclines. A study which involved CAF therapy done by Buzdar et.al showed a clinical response of 79.3% (Buzdar, 1999 and Burzykowski, 2008). But, the study involving cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) showed a response of 53% reduction while the pCr was 8% (Burzykowski, 2008). Though carcinomas are most prevalent among the disease conditions, carcinomas of the breast are most common in female populace succeeding cervical cancers (Denny, 2012). About 25% (1.67 million) of new cancer cases being diagnosed annually consisting of female-specific cancer cases, particularly breast carcinomas (Satija, 2014). Most commonly preferred combinations include cyclophosphamide and doxorubicin which can also be given as taxane-based formulations (Effects of chemotherapy and hormonal therapy, 2005). Main objectives of this study concentrated on the study

Table 1. Descriptive statistics for Age

Variable	N	Mean	Std. error Mean	Std. Deviation	Minimum	Q1	Median	Q3	Maximum
Age	173	51.15	0.979	12.88	18.00	43.0	52.00	60.0	81.00



Graph 1. Pie chart of Gender Prevalence

of characteristics and therapeutic statistics. In a patient populace of a tertiary care hospital. Apart from which this study aimed to analyze the effectiveness of NAC with anthracyclines in the downstaging reduction during 4-cycles of chemotherapy.

MATERIALS AND METHODS

The study was carried out in two tertiary care hospitals located in Hyderabad, India. The prime department of the study consist of Surgical and Medical Oncology. The design of the study is a prospective observational study, it was carried out for a period of six months. The sample size concurring to be 173 Case studies, the participants enrolled in the study consisted of inpatient and outpatient population in the hospital.

Study design: The study structure is carried out as retrospective and prospective observational studies to analyze the cancer characteristics, therapeutic approaches and the state of depression in Breast cancer patients.

Study period: The study period is planned in the timeline of July 2017 to February 2018.

Inclusion criteria:

Patient population consisting of conditions like the following

- Breast cancer
- Recurrent Breast cancer
- Metastatic Breast cancer
- Patients undergoing Adjuvant and Neoadjuvant chemotherapy.

Exclusion criteria:

Patient population with conditions like

- Fibroadenomas.
- Cystic mass.
- Hematomas.
- Fat necrosis.
- Hamartoma.

Statistical analysis: Statistical analysis was produced using an analytical tool Minitab® 17.2 and GraphPad Prism® 6.0. The descriptive statistics were presented either as Mean ± SD, the Standard error means, Variance, Skewness, Median, Q3, Maximum. The descriptive and graphical statistical analysis was done for Demographic data, clinical staging, the presence of recurrence, treatment types and menopausal status of the subjects.

Gender: Of 173 breast cancer patients, a rarity of 1.7% of male breast cancer cases was observed, remaining 98.3% were female breast cancer cases. The pie-chart obtained from the statistics is shown in Graph 1.

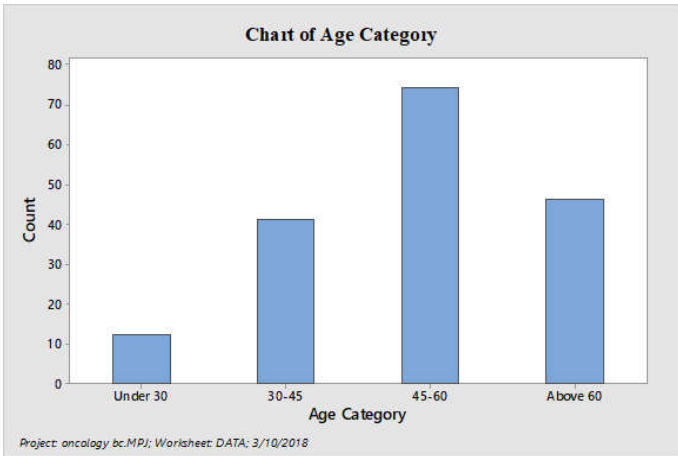
Descriptive statistics of age: The data for 173 breast cancer patients was collected from a tertiary care hospital and the Mean ± SD of the age of the subjects was found to be 51.15 ± 12.88 years with an age range of 18-81. The Minimum, Median, and Maximum ages were derived as 18.00, 52.00,81.00. The Standard Error was found to be 0.979. These descriptive statistics are shown in Table 1.
The population from the data was divided into age groups from below 30 to above 60 with the class interval of 15 in each class in the two groups between the above-mentioned class. The simple histogram chart of the same is shown in Graph 2.

Treatment Type

The study involving treatment type was merged with the clinical staging to analyze the preference of adjuvant and neoadjuvant chemotherapy in different clinical stages. The data is shown in a tabulated form in Table 2.

Prevalence of recurrence: The incidence of recurrence was observed of different types of recurrences in the considered population of patients. There were 4.04% of local carcinoma recurrences, 19.07% were found to be metastatic recurrences,

and 14.45% were Her2Neu positive metastatic recurrences. This data is represented in Table 3.



Graph 2. Population in different age groups

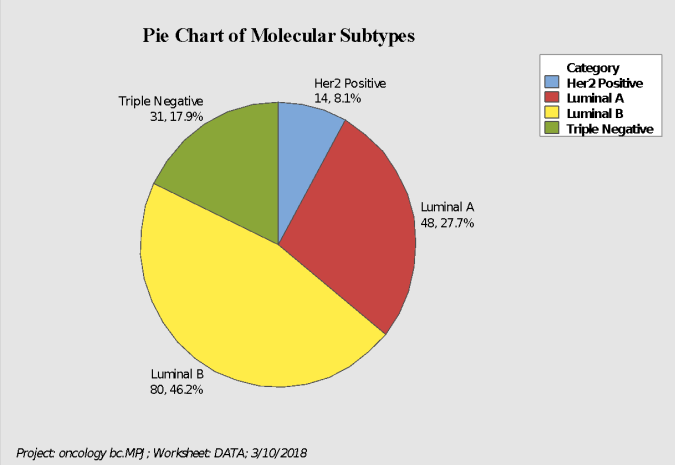
Table 2. Treatment type at different clinical stages

Clinical Stage	Adjuvant Therapy	Neoadjuvant Therapy
STAGE 0	0.00	0.00
STAGE 1	2.31	0.00
STAGE 2A	18.23	5.46
STAGE 2B	9.82	13.87
STAGE 3A	6.93	3.57
STAGE 3B	8.67	0.00
STAGE 4	30.52	0.00

Table 3. Types of recurrences and their prevalence

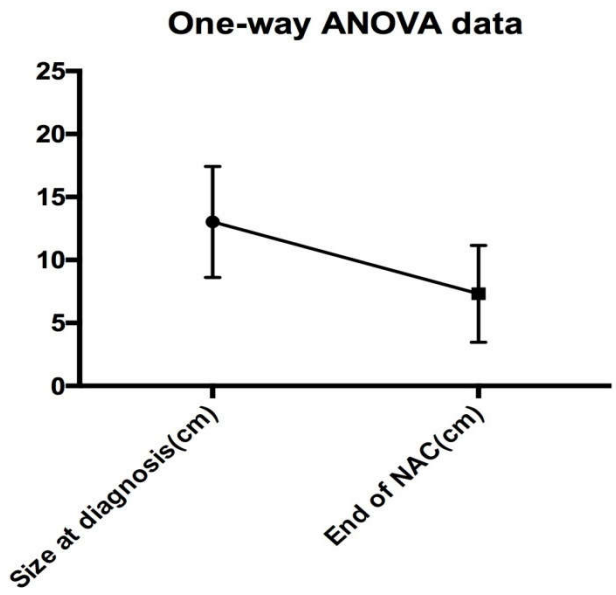
Type of recurrence	Count	Percentage
Locally Recurrent	7	4.04
Recurrent Metastatic	33	19.07
Recurrent Metastatic Her2 positive	25	14.45

Molecular Subtypes: Immunohistochemistry analysis showing molecular subtypes of Luminal A, Luminal B, Basal-like/Triple negative and Her2Neu positive breast cancer incidence was analyzed using simple statistical analysis. The incidence of Luminal A being 27.7%, Luminal B was found to 46.2%, Triple Negative carcinomas occurring in 17.9% of patients and 8.1% of the population in this study was found to be Her2Neu Positive. The pictorial description of the same is represented in Graph 3.

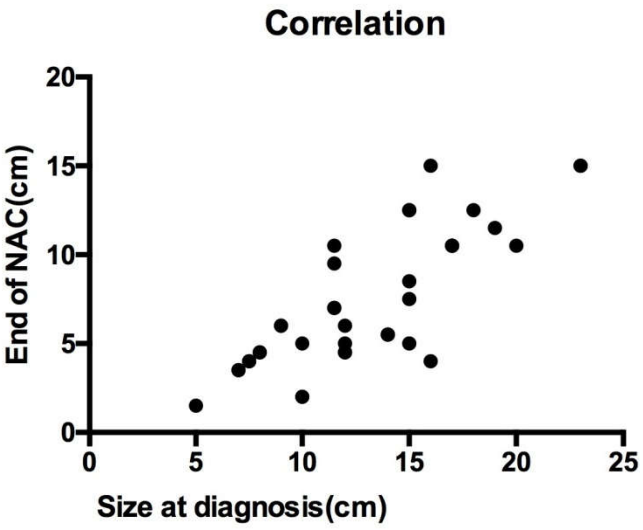


Graph 3. Molecular Subtypes of Breast cancer

Neoadjuvant therapy with Doxorubicin: 39 patients were given Doxorubicin is as Neoadjuvant therapy (NAC) out of 173 patients for 4 cycles before the surgery, the cycles are administered for every 3-week interval. The significant change in the tumor size (measured in cm) of 39 patients undergoing NAC. The line graph of the same is shown in Graph 5. One way ANOVA was performed on the data for the tumor size outcomes and the p-value was found to be 0.0001 (p-value <0.05) which suggests that there is a significant difference in tumor size after 4 cycles of Doxorubicin. Graph 6. Shows the correlative graph of tumor size at the time of diagnosis in comparison to the time of last (fourth cycle) dose of doxorubicin in neoadjuvant regimen.



Graph 5. Tumor mean size at different cycles of Doxorubicin.



Graph 6. Correlation between tumor sizes before and after neoadjuvant chemotherapy

DISCUSSION

Breast cancer is one of the highly prevalent female specific carcinomas, however, the rarity of male breast cancers is observed [21]. Though the incidence can be considered negligible, the incidence of male breast carcinomas was

increased significantly over the decades. The outcomes of this study have shown 1.7% male breast cancer cases, remaining 98.3% of the data having female breast carcinomas. The Mean ± SD of the age of 173 subjects was found to be 51.15 ± 12.88 years with an age range of 18-81. The Minimum, Median, and Maximum ages were derived as 18.00, 52.00, 81.00. Immunohistochemistry analysis showing molecular subtypes of Luminal A, Luminal B, Basal-like/Triple negative and Her2Neu positive breast cancer incidence was analyzed using simple statistical analysis. The incidence of Luminal A being 27.7%, Luminal B was found to 46.2%, Triple Negative carcinomas occurring in 17.9% of patients and 8.1% of the population in this study was found to be Her2Neu Positive.

The prevalence of treatment type choice in different stages of cancer was studied and the preference of Neoadjuvant therapy at Stage II A, Stage II B, and Stage IIIA in 3.46 %, 13.87% and 0.57% of the patient population respectively. Neoadjuvant chemotherapy has proved appealing potential benefits over the classic adjuvant therapy. Of all the pros from the neoadjuvant chemotherapy, the only proven benefit is to enhance the surgical approach, either by shrinking inoperable cancer to an operable one or by aiding them in making the choice of surgery to breast-conserving surgery over mastectomy. Studies have shown that there's a notable decrease in the need for mastectomy in major cases. Around 17.4% of patients receiving neoadjuvant chemotherapy(NAC), including 4% of patients with clinical stage I carcinoma, 17.8% of patients with stage II disease, and 41.6% of patients with stage III disease. The use of neoadjuvant chemotherapy has significantly increased over time from a 12.2% to 24.0%, especially among patients with further locally advanced cancers. Rates have expanded from 12.9% to 39.3% in patients with stage IIIA, from 72.3% to 86.4% in patients with stage IIIB, and from 30.1% to 59.3% in patients with stage IIIC cancers (Beriwal, 2006). The effects of Doxorubicin neoadjuvant therapy were analyzed with respect to tumor size after each cycle of NAC.The significant change in the tumor size (measured in cm) of 39 patients undergoing NAC. One way ANOVA was performed on the data for the tumor size outcomes and the p-value was found to be 0.0001 (p-value <0.05) which suggests that there is a significant difference in tumor size after 4 cycles of Doxorubicin.

Conclusion

The use of Doxorubicin for neoadjuvant therapy was found to be significantly beneficial in the reduction of tumor size of locally advanced breast cancers (LABC). This reduction in tumor size prior surgery helps in the choice of type of surgery being performed. It can result in avoiding the use of mastectomy and more preference for breast-conserving surgeries can be given.

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Annexure:

<table>
<tr><td colspan="5">BREAST CANCER</td></tr>
<tr><td colspan="3"></td><td colspan="2">Medical Record Number:</td></tr>
<tr><td colspan="5">BACKGROUND INFORMATION</td></tr>
<tr><td>Age at Diagnosis :</td><td colspan="4">Breast Cancer Site : □Left Breast □ Right Breast □ Bilateral</td></tr>
<tr><td colspan="5">Family History □ None □ 2nd Degree Relative □ 1st Degree Relative □ Multiple Relatives</td></tr>
<tr><td colspan="5">Definitive Breast Surgery : Date : (____/____/____) Type : □ Lumpectomy □ Mastectomy □ Mastectomy/Immediate Recon</td></tr>
<tr><td colspan="3"># Lymph nodes removed (total - sentinel node + dissection) :</td><td colspan="2"># Lymph Nodes Positive</td></tr>
<tr><td>Axilllary Dissection : □ Yes(____/____/____) □ No</td><td colspan="4">Sentinel Node Biopsy : □ Yes (____/____/____) □ No</td></tr>
<tr><td colspan="5">Notable Surgical Findings / Comments :</td></tr>
<tr><td colspan="5">Tumour Type : □ Infiltrating Ductal □ Infiltrating lobular □ Mixed Lobular / Ductal □ Other</td></tr>
<tr><td colspan="3">T Stage : □ T1 □ T2 □ T3 □T4a □T4b □T4c □T4d</td><td colspan="2">N Stage : □ N0 □ N1 □ N2 □N3</td></tr>
<tr><td colspan="3">Stage : □ 0 □ I □ II □III</td><td colspan="2">Oncotype DX recurrence score (if Applicable) :</td></tr>
<tr><td>ER Status : □ Postive □ Negative</td><td colspan="2">PR Status : □ Postive □ Negative</td><td colspan="2">HER2 Status : □ Postive □ Negative</td></tr>
<tr><td colspan="5">Major Comorbid Conditions :</td></tr>
<tr><td colspan="5">Echocardiogram or MUGA result prior to chemotherapy (if obtained) : EF= %</td></tr>
<tr><td colspan="3">ADJUVANT / NEOADJUVANT TREATMENT PLAN</td><td colspan="2">ADJUVANT / NEOADJUVANT TREATMENT SUMMARY</td></tr>
<tr><td>Height : _____inch/ Cm</td><td colspan="2">Pre-treatment Weight:_____ lb /kg</td><td colspan="2">Post-treatment Weight: _____ lb /kg</td></tr>
<tr><td>Pre-Treatment BSA :</td><td colspan="2">Date Last Menstrual Period : (____/____/____)</td><td colspan="2">Date Last Menstrual Period : (____/____/____)</td></tr>
<tr><td colspan="3">Treatment on Clinical Trial : □ Yes □ No</td><td colspan="2">Pre-operative Chemo Administered : □ Yes □ No</td></tr>
<tr><td colspan="5">Start Date : (____/_____/_____)</td></tr>
<tr><td>Chemotherapy Drug Name</td><td>Route</td><td>Dose</td><td>Schedule</td><td></td></tr>
</table>

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